CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLONICAMID

Chemical Code # 5886, **Tolerance #** 52964
SB 950 # New A.I.

July 12, 2004
Revised: 4/28/05

I. DATA GAP STATUS

Combined toxicity (chronic/onco), rat:	No data gap, no adverse effect
Subchronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Subchronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity (Hen):	Not submitted, not required at this time[a]

a - Acceptable acute and subchronic neurotoxicity studies in rat.
Toxicology one-liners are attached.

All record numbers through 216061 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T050428
Revised by T. Moore, 7/12/04; M. Silva, 4/28/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

DISCUSSION OF POSSIBLE ADVERSE ONCOGENIC EFFECTS IN RATS AND MICE:

52964 - 050 216024 "FLONICAMID (IKI-220): Rationale for Regulation by Reference Dose," (Cohen, S.M., Hardisty, J.F., McCarty, J.D.; FMC Corporation, Agricultural Products Group, Princeton, NJ; Document #: flonicamid 04-04, 8/31/04). This report contains a complete discussion (along with a presentation of summary data) on the mechanism and potential for oncogenicity of flonicamid. All studies discussed in this report were presented for review to DPR. Many of the potential adverse effects, primarily regarding the incidence of nasal and lung cancer in rats and mice, respectively, were initially noted in worksheets provided by USEPA. Upon re-evaluation of the noted effects, the nasal cancers in rats were found to originate in the nasal-lacrimal duct, which is more common than the squamous cell carcinomas. The nasolacrimal duct tumors were determined to be unilateral and not bilateral which indicated they were spontaneous and not due to treatment. Based on the low spontaneous incidence of these tumors in humans versus rats, the potential for their initiation in humans after flonicamid exposure, were negligible. Lung tumors (observed only in mice) appeared to be due to mitogenesis, non-linear, non-genotoxic mode of action for which a threshold dose has been established. Historical controls were presented for all potential adverse effects. Included also were complete discussions of all questions raised by USEPA. This information is supplemental. No worksheet was performed for this data volume. Silva, 2/2/05.

COMBINED, RAT

** 52964 - 0071 - 0077 216045 - 216051 "IKI-220 Technical: Combined Chronic Toxicity and Carcinogenicity Study in Rats with Amendments 1 and 2 (see page of this worksheet for DPR volume/record #s for supplemental data)," (Kuwahara, M.; The Institute of Environmental Toxicology, Ibaraki, Japan; Laboratory Project ID #: IET 98-0142; 12/12/02, 4/7/04 and 10/27/04). IKI-220 technical (98.7% pure) was fed in diet to SPF Wistar (Jcl:Wistar) rats at 0, 50, 100, 200 and 1000 ppm (Males: 52/dose - Main Group & 14/dose Satellite Group I; 10/dose Satellite Group II); at 0, 200, 1000 and 5000 ppm (Females: 52/dose - Main Group & 14/dose Satellite Group I;10/dose Satellite Group II). Satellite Group II was terminated at 6 months, Satellite Group I was terminated at 12 months and the Main Group animals were terminated at 2 years. Test substance intake for males was 1.84, 3.68, 7.32 and 36.5 mg/kg/day and for females was 8.92, 44.1 and 219 mg/kg/day (values were for main group only). Chronic NOEL = 200 ppm–M, 1000 ppm–F (Mortality was slightly increased in the high doses at termination. At 5000 ppm there was an increase in red adhesive substance on the integument (F). Females had an increased incidence in skin masses at 5000 ppm. Males at 1000 had decreased spontaneous motor activity and bradypnea, increased grooming and decreased rearing (F: 5000 ppm). Decreased specific gravity (M: 1000 ppm, F: 5000 ppm), increased volume and protein (M:1000 ppm) occurred in urine. Related to tubular basophilic change, granular casts were found in dilated tubules (M). Decreases in Ht, Hb and RBC count and increased MCHC were observed (F:5000 ppm). Liver and kidney weights were increased in both sexes at 1000 (M) and 5000 ppm (F). Effects to liver (dark color and accentuated lobular pattern) and eye discharge were observed (F 5000 ppm). Increases in atrophy of retina and cataracts occurred and blood chemical parameters were affected (F: 5000 ppm). Increases in cytoplasmic vacuolation and in brown pigment of proximal tubular cells occurred (F: 5000 ppm). Females at 5000 ppm had statistically significantly decreased body weight and food consumption and low food efficiency. No adverse effect. (No treatment-related oncogenicity, however an increased (non-statistically significant) incidence in nasolacrimal duct squamous cell tumors (M:1000, F: 5000 ppm) and an increase in hematopoiesis in the bone marrow were observed (F: 5000 ppm).) Acceptable. (Silva, 4/11/05)
Additional volumes and reports were submitted with the main combined rat study reviewed above. These volumes were as follows:

52964 - 0072 216046 "Response to EPA Review and Submission of Supplemental Data to Report:: Historical Control Data for IKI-220 Technical: Combined Chronic Toxicity and Carcinogenicity Study in Rats," (M. Kuwahara; Document #: IET 98-0142 Supplement 1;12/12/02 Original; 5/18/04

Supplement). This volume contains neoplastic and non-neoplastic lesion incidence historical control data for both sexes of Wistar rat from 4 different IET combined (oncogenicity/chronic) studies. These data were examined and compared to the definitive study findings. Incidences of effects that were greater than historical control incidences were noted in the DPR worksheet by italics in the histopathology tables. (Silva, 4/11/05)

52964 - 0073 216047 "Response to EPA Review and Submission of Supplemental Data to Report: Historical Control Data (RCC Ltd., Itingen, Switzerland) for IKI-220 Technical: Combined Chronic Toxicity and Carcinogenicity Study in Rats," (M. Kuwahara; IET 98-0142 Supplement 2;12/12/02 Original; 6/25/04 Supplement 2). This volume contains "Historical Control Data on Neoplastic Findings in Wistar Rats (Planned Sacrifice After 103 Weeks)." The data were examined in relation to the definitive study, where squamous cell tumors may have been a treatment-related effect. (Silva, 4/11/05)

52964 - 0074 216048 "IKI-220 Technical: Combined Chronic Toxicity and Carcinogenciity Study in Rats Histopathological Examination of the Nasal Cavity," (M. Kuwahara; IET 04-0067; 8/19/04). This volume contains an analysis of the nasal cavity histopathology from the original study. Historical control range for this effect was less than the combined incidence of squamous cell tumors in the definitive study for both sexes [Male Incidence: 9/255, 3.5% (mean); 0 - 10% (range) and Female Incidence: 2/254, 0.8% (mean); 0 - 4.1% (range)] based on results from 5 toxicity studies in Jcl: Wistar rats performed at IET, Ibaraki, Japan (1982 - 1987). All animals terminated at 52 weeks and in the104 week portions of the study had all nasal and paranasal tissues examined histologically. For animals that had not been examined in the original study, tissues were prepared and examined for histopathology. There appeared to be an increase in incidence in nasolacrimal duct squamous cell tumors at 1000 ppm in males and at 5000 ppm in females (when compared to historical controls). The report speculated that these effects may be due to chronic inflammation of the nasolacrimal duct throughout treatment. Data show that chronic inflammatory changes were observed in the nasolacrimal duct with or without squamous cell metaplasia and/or hyperplasia of lining epithelium. Squamous cell metaplasia and hyperplasia were lesions usually accompanied by chronic inflammation and the incidences of these non-neoplastic lesions in males were greater than those in females (as were the squamous cell tumors). The report stated on page 17 that since the majority of the tumors and non-neoplastic effects occurred unilaterally that they were spontaneous and not treatment related. If they were treatment-related they would have occurred bilaterally in the paired organs. Additionally, the tumor incidences were not statistically significantly increased in either sex at any dose. However; due to the increase in incidence in nasolacrimal duct tumors (compared to historical controls and internal controls) this effect will be flagged as a possible adverse effect. (Silva, 4/11/05)

52964 - 0075 216049 "IKI-220 Technical: Combined Chronic Toxicity and Carcinogenciity Study in Rats," (M. Kuwahara; IET 98-0142; 8/16/04). This volume contains discussion of questions concerning the bone/bone marrow effects and cerebellar granular tumors observed in the original study. This document was a response to U.S. EPA questions about an apparent increase incidence in hematopoiesis in bone marrow (femur). This effect was observed primarily as a compensatory response for a decrease in blood cell components due to spontaneous lesions at other sites and observed mainly in animals receiving unscheduled necropsies. Tables 1 and 2 (pages 10 - 11) in the volume list the causes or probable causes for increased hematopoiesis in the bone marrow (femur). The U.S. EPA reviewer asked whether fluorine from flonicamid could cause the bone effects. Metabolism studies have shown that free fluorine is not released and therefore the bone effects were not related to free fluorine. In this document the U.S. EPA also questioned whether the cerebellar granular cell tumors (observed histopathologically) were treatment related. It was reported that GCT involving the meninges of the brain is the most frequently reported benign neoplasm occurring in many strains of rat. Historical controls obtained from 38 2-year studies in Wistar rats (1981 - 2000) at RCC Ltd., Switzerland showed a range of 0 - 7.14% (M) and 0 - 4.35% (F). The report concluded that since GCTs of meninges are observed only microscopically, small ones may be included in the sections examined only by chance. The tumors do not metastasize and are possibly underreported. Thus their true incidence is not really known. The report considered these observations to be incidental and unrelated to treatment. DPR considers the GCTs to be marginally increased in females when compared to historical controls but essentially equivocal. (Silva, 4/11/05)

52964 - 0076 216050 “IKI-220 Technical: Combined Chronic Toxicity and Carcinogenciity Study in Rats, Histopathological Examination of Bone Marrow,” (M. Kuwahara; IET 04-0074; 8/31/04). This volume contains a detailed examination of bone marrow lesions from the original study in both sexes of rat. In addition there were individual data from histopathology of bone marrow from the terminal kill after 104 weeks of treatment. (Silva, 4/11/05)

52964 - 0077 216051 “IKI-220 Technical: Combined Chronic Toxicity and Carcinogenciity Study in Rats,” (M. Kuwahara; IET 98-0142: revision to Supplement 1; 8/27/04). This volume contains historical control data for neoplastic and non-neoplastic control Wistar rats of both sexes from IET combined studies. In addition there are incidences for neoplastic and non-neoplastic nasal cavity lesions in Wistar rats from IET combined studies. (Silva, 4/11/05)

CHRONIC TOXICITY, DOG

Subchronic Oral Toxicity Study:

52964-0013; 208802; “A 90-Day Oral Toxicity Study in Dogs with IKI-220 Technical”; (W.E. Ridder, M. Watson; Toxicology and Pharmacology, Ricerca LLC, Painesville, OH; Report No. 011509-1; 9/5/01); Four beagle dogs/sex/group received 0, 3, 8, or 20 mg/kg/day of IKI-220 Technical (lot no. 9809, purity: 98.7%) in capsules for 13 weeks. An additional group of 4 females received 50 mg/kg/day of the test material for the same duration. Both the males and females in the 20 mg/kg group and the females in the 50 mg/kg group demonstrated treatment-related signs of vomiting. Ataxia was also noted for some of the animals in these groups. Incidences of diarrhea and excessive salivation were observed for the females in the high dose group. The females in the high dose group were so affected as to refuse to eat the certified dog chow. One female in the 50 mg/kg was euthanized due to severe anorexia on study day 20. Food consumption was significantly lower for the females in the 50 mg/kg group ($p<0.05$). There were no apparent treatment-related effects noted in the ophthalmology examination or the urinalysis. In the hematology evaluation, the mean red blood cell count for the 50 mg/kg females at 7 weeks was less than that of the control ($p<0.01$). The hemoglobin and hematocrit values for these females at this time point demonstrated a significant trend ($p<0.01$). The percentage of reticulocytes in the blood of these females was significantly increased at 7 weeks and demonstrated a significant trend at the termination of the study. In the clinical chemistry assessment, the cholesterol concentration in the serum was increased for the 50 mg/kg females at 7 weeks. In the necropsy examination, the mean absolute and relative thymus weights of the 20 mg/kg males were lower than those values for the controls ($p<0.01$). The mean relative lung weight for the 50 mg/kg females was greater than that of the controls ($p<0.05$). In the histopathology examination, 2 of the 4 females in the 50 mg/kg group demonstrated vacuolation in the tubules of the kidney. Two animals each among the females in the 20 and 50 mg/kg groups exhibited focal interstitial inflammation in the lungs. **No adverse effect indicated. Subchronic NOEL:** (M/F) 8 mg/kg/day (based upon the manifestation of clinical signs in the 20 mg/kg treatment group). **Study acceptable.** (Moore, 5/13/04)

Definitive Study:

** 52964 - 0064 216038 “A 52-Week Oral Toxicity Study in Dogs With IKI-220 Technical, Amended Report,” (Ridder, W.E., Watson, M.; Toxicology and Pharmacology, Ricerca Biosciences, LLC, Painesville, OH; Document #: 012075-1-1; 11/15/02 (amended report 1/2/03)). Flonicamid technical (IKI-220, *N*-cyanomethyl-4-trifluoromethyl nicotinamide: 98.7% pure) was administered by capsules to beagle dogs (6/sex/dose) at 0 (capsule only), 3, 8 and 20 mg/kg/day for 1 year (365 consecutive days). NOEL = 8 mg/kg/day (Body weight gains were significantly decreased in females at 20 mg/kg/day during weeks 2-4. Although the body weight gains were not statistically different from controls for the remainder of the study, the body weight gain decrease was 30% at termination for females at 20 mg/kg/day (4.90 kg for controls vs. 3.41 kg at 20 mg/kg/day). Males at 9 and 12 months had statistically significantly increased MCV and MCH and at 12 months increased reticulocytes (%) at 20 mg/kg/day. NOTE that at pretest males at 20 mg/kg/day had a statistically significantly decreased RBC, HGB and HCT. Throughout the test, however these parameters were comparable to controls.

Females at 9 months had statistically significantly decreased RBC, HGB and HCT at ≥ 8 mg/kg/day. At 12 months females had statistically significantly increased MCH and Reticulocytes (%) at 20 mg/kg/day. The increases in reticulocytes, and in corpuscular and hemoglobin effects in both sexes indicated that IKI-220 had effects in circulating red blood cells. Males had increased total protein from 6 months at 20 mg/kg/day. Male absolute and relative kidney weights were statistically significantly increased at 20 mg/kg/day. Female absolute thyroid (+ parathyroid), heart, and liver weights were increased at 20 mg/kg/day. There was no histopathology associated with these increases.) No adverse effect. Acceptable. (Silva, 2/28/05)

ONCOGENICITY, MOUSE

**** 52964 - 0065, 0066, 0067 216039, 216040, 216041** "Volume 0065: An Oncogenicity Study in Mice with IKI-220 Technical (Volume 0066: supplemental data); Volume 0067: IKI-220: Discussion on Lung Finding Observed in Mouse Oncogenicity Study," (Ridder, W.E., Watson, M. for volumes 0065 & 0066; Nomura, M. for volume 0067; Toxicology and Pharmacology, Ricerca Biosciences, LLC, Painesville, OH; Safety Science Group, Safety Science Research Laboratory, Central Research Institute, Ishihara Sangyo Kaisha, Ltd., Shinga-ken Japan; Document #s: 011885-1, 011885-1-2 & AN-2203 for volumes 0065, 0066 & 0067, respectively; 1/3/03, 6/11/04 & 1/21/03 for volumes 0065, 0066 & 0067, respectively). Flonicamid technical (IKI-220 [*N*-cyanomethyl-4-trifluormethyl nicotinamide]: 98.7% pure) was fed in diet to Charles River Crl:CD-1®(ICR)BR VAF/Plus mice (60/sex/dose) at 0, 250, 750 and 2250 ppm (equivalent doses: M = 29, 88, 261 mg/kg/day; F = 38, 112 and 334 mg/kg/day) for 18 months. An additional 20/sex/dose were treated at 0, 250 and 2250 ppm to provide 10/sex/dose at the 26 and 52 week interim sacrifices. Systemic NOEL = 250 ppm (Mean and relative food consumption was intermittently statistically significantly decreased in both sexes throughout the study at 2250 ppm. There was a statistically significant decrease in monocytes in males and an increase in eosinophils in females at 2250 ppm. There was a dose related increase in gross liver lesions in males and in gross lung lesions in both sexes at most doses. At week 52, males had a statistically significant increase in absolute liver weights and at week 26 there was an increase in relative liver weights in both sexes at 2250 ppm. At termination males had decreased absolute brain weights at 2250 ppm and females had significant trends toward decreasing absolute ovary weights. Males had significantly decreased relative kidney weights and females had significantly increased absolute and relative liver weights at 2250 ppm. Both sexes had significant trends toward increasing absolute and relative spleen and liver weights. There was a increase in non-neoplastic pathology in several organ systems, but primarily spleen, liver and lung in one or both sexes at ≥ 750 ppm. In addition, there was a dose-related increase in epithelial hypertrophy/hyperplasia in the terminal bronchioles and focal alveolar/bronchiolar hyperplasia that was observed at all doses and in both sexes.) Possible adverse effect: Oncogenicity NOEL < 250 ppm (There was an increase in alveolar/bronchiolar adenomas and carcinomas at all doses in both sexes.) This study is acceptable. Note that Supplemental studies in 52964-0067 indicated that the CD-1 mouse was more responsive for IKI-220 in terms of cell cycling in the terminal bronchioles than B6C3F1 or C57 mice or rats, using BrdU incorporation. Also, recovery from cycling occurred within one week in mice. Silva, 3/7/05

52964 - 0068, 0069 & 0070 216042, 216043, 216044 "Vol 0068: Dietary Carcinogenicity of IKI-220 Technical in Mice; Vol 0069: Pathology Sub-Report (Supplemental) for Dietary Carcinogenicity of IKI-220 Technical in Mice; Vol 0070: Historical Data for Dietary Carcinogenicity of IKI-220 Technical in Mice," (Nagaoka, T., Nakashima, N.; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima, Japan; The Institute of Environmental Toxicology, Ibaraki, Japan; 1/22/04, 3/30/04, 1/22/04 for volumes 0068, 0069 & 0070, respectively). Flonicamid technical (IKI-220: 98.7% pure) was fed in diet to Charles River Crj:CD-1®(ICR)BR mice (50/sex/dose) at 0, 10, 25, 80 and 250 ppm (equivalent doses: M = 1.20, 3.14, 10, 30.3 mg/kg/day; F = 1.42, 3.67, 11.8, 36.3 mg/kg/day) for 78 weeks. Systemic NOEL = 80 ppm (There was an increase in lung hyperplasia and hypertrophy (both sexes) and liver fatty change in centrilobular hepatocytes (F) at 250 ppm. There was a statistically significant decrease in absolute kidney weights in females at 250 ppm. There was a statistically significant increase in lung masses--pulmonary adenomas and carcinomas in males at 250 ppm.) Not acceptable (There were numerous deficiencies in this study (see A., above). There were no interim kills, nor were all target

organs examined and weighed as recommended by FIFRA Guidelines.), not upgradeable. Possible adverse effect indicated (There was a statistically significant increase in pulmonary adenomas and carcinomas in males at 250 ppm. Silva, 4/29/05

REPRODUCTION, RAT

Rangefinding Study:

52964 - 0062 216036 "IKI-220 Technical: Reproductive Toxicity Study in Rats Preliminary Study (Amended Report)," (Takahashi, K.; Institute of Environmental Toxicology, Ibaraki, Japan; Laboratory Study #: IET 99-0084; 2/25/02; Final Report Amended 12/26/02). Flonicamid technical (*N*-cyanomethyl-4-trifluoromethylnicotinamide; 98.7% pure) was administered via diet to (SPF) Wistar (Jcl:Wistar) rats (8/sex/dose) at 0 (Basal diet), 50, 200, 1000 or 2000 ppm for 10 weeks (3 weeks premating, 1 week mating, 3 weeks gestation, 3 weeks lactation) of the parental generation. Actual test substance intake was, for males and females respectively, 2.86 and 5.28 mg/kg/day at 50 ppm, 11.49 and 20.8 mg/kg/day at 200 ppm, 57.7 and 103.7 mg/kg/day at 1000 ppm and 114.2 and 214 mg/kg/day at 2000 ppm. Parental NOEL = 50 ppm (Increased incidence in kidney gross and histopathology at $\geq$ 200 ppm and in kidney absolute and relative weights at 2000 ppm in males. These effects were not observed in females.) Reproductive NOEL > 2000 ppm and Pup NOEL > 2000 ppm. Although the study reported a NOEL of 200 ppm for systemic effects, this reviewer considers 50 ppm to be the NOEL, since the histopathology observed in all males at $\geq$ 1000 ppm, were also observed in 5/8 animals (statistically significant) at 200 ppm. Possible adverse effect for kidney effects. These data are supplemental. Silva, 2/10/05

Definitive Study:

** 52964 - 0063 216037 "IKI-220 Technical: Reproductive Toxicity Study in Rats," (Takahashi, K.; Institute of Environmental Toxicology, Ibaraki, Japan; Laboratory Study #: IET 99-0085; 12/12/02). Flonicamid technical (*N*-cyanomethyl-4-trifluoromethylnicotinamide; 98.7% pure) was administered via diet to (SPF) Wistar (Jcl:Wistar) rats (24/sex/dose) at 0 (Basal diet), 50, 300 and 1800 ppm for 10 weeks (premating), mating, gestation, lactation and weaning for 2 generations through weaning of the F2 pups. Actual test substance intake was as follows for P males, F1 males, P females and F1 females in that order: 3.07, 3.39, 4.67, and 4.95 mg/kg/day (50 ppm), 18.3, 20.7, 28.2 and 30.5 mg/kg/day (300 ppm) and 109.1, 124.8, 163.8 and 176.8 mg/kg/day (1800 ppm). **Parental NOEL = 300 ppm** (Body weights were decreased at 1800 ppm for P generation males during weeks 0 - 1 of the premating period and body weight gains were increased at $\geq$ 300 ppm in P parental females during LD 0 - 21. Food consumption was decreased in P females during GD 0 - 7 and 7 - 14 and LD 0 - 7 at 1800 ppm. Absolute kidney weights were statistically significantly increased at 1800 ppm in P and F1 males. Absolute thyroid weights of P males were increased at 1800 ppm. Absolute testes and ovary weights in F1 parents were statistically significantly decreased at 1800 ppm. Relative kidney weights were increased in P males at 1800 ppm and in F1 males at $\geq$ 300 ppm. Relative thyroid weights were increased in P males at 1800 ppm. Relative seminal vesicle weights were increased in F1 males at 1800 ppm. In parental females, relative P adrenal weights were increased and relative ovary weights were decreased at 1800 ppm and relative F1 liver, kidney and spleen weights were increased at 1800 ppm. Kidney histopathology in both generations of males ($\geq$ 300 ppm) and females (1800 ppm) was increased. At 300 ppm males had significantly increased incidence of hyaline droplets in kidney proximal tubular cells, containing $\alpha 2\mu$-globulin [see record 208800].) **Reproductive NOEL = 300 ppm** (There was a slight but statistically significant increase in duration of gestation in P females at 1800 ppm. Binding of IKI-220 to human estrogen receptor was very low. LH and FSH were significantly increased and 17β-estradiol was lower (NS) in F1 parental females.) **Pup NOEL = 300 ppm** (There was a statistically significant increase in F1 pups' time to vaginal opening (32.6 d control versus 34.1 d at 1800 ppm). This effect was not repeated in the F2 generation. There was a statistically significant decrease in F1 weanling absolute and relative uterine weights at 1800 ppm (of 21 pups assessed).) No adverse reproductive effect, however a possible adverse for kidney pathology occurred in both sexes. Acceptable. Silva, (2/23/05)

TERATOLOGY, RAT

52964-0015 208804 Hojo, H., "IKI-220 Technical: a teratology study in rats," Institute of Environmental Toxicology, Ibaraki, Japan, 2/21/02. Laboratory Study #: IET 00-0023. Twenty-four mated Jcl:Wistar dams/group were dosed on gestation days 6 to 19 with flonicamid (IKI-220 Technical) in 1% CMC suspensions in a standard teratology study at dose levels of 0, 20, 100, and 500 mg/kg/day. Maternal NOEL = 100 mg/kg/day (elevated absolute and relative liver weights associated with centrilobular hypertrophy; vacuolation of the proximal tubules in kidneys). Developmental toxicity NOEL = 100 mg/kg/day (marked increase in cervical rib incidence). **No adverse effects.** Study previously not acceptable, possibly upgradeable with documentation of stability of test article for 14 days. The submitted teratology dose range-finding study (vol. 52964-0038, rec. no. 212288) "IKI-220 Technical: a teratogenicity study in rats, preliminary study (IET 00-0022)"] provided the needed documentation. **Study acceptable.** (Aldous, June 4, 2004, upgraded, Moore, 7/9/04)

52964 - 0038; 212288; "IKI-220 Technical: A Teratogenicity Study in Rats, Preliminary Study"; (H. Hojo; The Institute of Environmental Toxicology, Misukaido-shi, Ibaraki 303-0043, Japan; Project ID. IET 00-0022; 2/21/02); Eight mated female Wistar rats/group were dosed orally by gavage with 0, 30, 100, 300 or 1000 mg/kg/day with IKI-220 Technical (lot. no. 9809, purity: 98.7%) from day 6 through day 19 of gestation. Six of the dams in the 1000 mg/kg group died between day 9 and day 13 of gestation. The mean body weight gain for the 1000 mg/kg females at days 9 and 12 of gestation was less than that of the control. Mean food consumption for these dams was likewise less than that of the controls over this same time period. There were no apparent effects upon the development of the fetuses. **No adverse effects indicated. Study supplemental** (study was performed for the purpose of dose range-finding). (Moore, 7/9/04)

TERATOLOGY, RABBIT

Rangefinding Study:

52964 - 0060 216034 "IKI-220 Technical: A Teratogenicity Study in Rabbits Preliminary Study," (Takahashi, K.; Institute of Environmental Toxicology, Ibaraki, Japan; Laboratory Study #: IET 00-0024; 2/21/02). Flonicamid technical (98.7% pure) was administered via oral gavage to artificially inseminated SPF Japanese White rabbits (Kbl:JW) (6/dose) at 0 (1% sodium carboxymethyl cellulose), 3, 10 and 30 mg/kg/day during gestation days 6 through 27. Maternal NOEL = 10 mg/kg/day (There were slight effects on body weight, body weight gain, clinical signs, abortion (2/6 does at 30 mg/kg), food consumption, gravid uterine weights and placental weights at 30 mg/kg/day.) Developmental NOEL = 10 mg/kg/day (There were lowered sex ratios, and fewer implants and live fetuses at 30 mg/kg/day.) There were no major deficiencies in this study. It was for the purpose of dose rangefinding for the definitive study. No adverse effect indicated. These data are supplemental. Silva, 2/10/05

Definitive Study:

** 52964 - 0061 216035 "IKI-220 Technical: A Teratogenicity Study in Rabbits," (Takahashi, K.; Institute of Environmental Toxicology, Ibaraki, Japan; Laboratory Study #: IET 00-0025; 2/21/02 & final report amended 11/28/02). Flonicamid technical (98.7% pure) was administered via oral gavage to artificially inseminated SPF Japanese White rabbits (Kbl:JW) (25/dose) at 0 (1% sodium carboxymethyl cellulose), 2.5, 7.5 and 25 mg/kg/day during gestation days 6 through 27. Maternal NOEL = 7.5 mg/kg/day (Body weight gains at 25 mg/kg/day were statistically significantly decreased during the interval of GD 6 - 28 (throughout treatment). At 25 mg/kg/day there was statistically significantly decreased food consumption on GD 9 - 12, 12 - 15, 15 - 18 and 18 - 21. Developmental NOEL = 25 mg/kg/day (There were no treatment-related effects at any dose.) Acceptable. No adverse effect. (Silva, 2/11/05)

GENE MUTATION

** 52964-0078 216052 *"Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay With TFNA," (Wollny, H-S., RCC Cytotest Cell Research GmbH, Rossdorf, Germany, Document #: 716901; 9/6/02). TFNA (99.4% pure) was used *in vitro* on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA^{--} at 0 (DMSO), 33, 100, 333, 1000, 2500, and 5000 ug/plate (triplicate plates) to test mutagenicity in 2 experiments (I pour plate; II pre-incubation test for 60 minutes) both with and without S9 metabolic activation. All strains and all exposure levels of TFNA were negative with and without S-9. The positive controls were functional. Acceptable. No adverse effect. Silva, 4/12/05

** 52964-0079 216053 *"Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay With TFNA-AM," (Wollny, H-S., RCC Cytotest Cell Research GmbH, Rossdorf, Germany, Document #: 716904; 9/6/02). TFNA-AM (100% pure) was used *in vitro* on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA^{-} at 0 (DMSO), 33, 100, 333, 1000, 2500, and 5000 ug/plate (triplicate plates) to test mutagenicity in 2 experiments (I pour plate; II pre-incubation test) both with and without S9 metabolic activation. All strains and all exposure levels of TFNA-AM were negative with and without S-9. No adverse effect. Acceptable. Silva, 4/12/05

** 52964-080 216054 *"Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay With TFNG-AM," (Wollny, H-S., RCC Cytotest Cell Research GmbH, Rossdorf, Germany, Document #: 716902; 9/6/02). TFNG-AM Technical (N-(4-Trifluoromethylnicotinoyl) glycinamide; 99.5% pure) was used *in vitro* on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA at 0 (DMSO), 33, 100, 333, 1000, 2500, and 5000 ug/plate (triplicate plates) to test mutagenicity in 2 experiments (I pour plate; II pre-incubation test) both with and without S9 metabolic activation. All strains and all exposure levels were negative with and without S-9. No adverse effect. Acceptable. Silva, 4/12/05

** 52964-0081 216055 *"Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay With TFNA-OH," (Wollny, H-S., RCC Cytotest Cell Research GmbH, Rossdorf, Germany, Document #: 716905; 9/6/02). TFNA-AM Technical (6-hydroxy-4-Trifluoromethylnicotinic acid;100% pure) was used *in vitro* on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA^{-} at 0 (DMSO), 33, 100, 333, 1000, 2500, and 5000 ug/plate (triplicate plates) to test mutagenicity in 2 experiments (I pour plate; II pre-incubation test [60 minute preincubation]) both with and without S9 metabolic activation. All strains and all exposure levels of TFNA-AM were negative with and without S-9. No adverse effect. Acceptable. Silva, 4/12/05

** 52964-0082 216056 "TFNG: Bacterial Reverse Mutation Test," (May, K.; Huntingdon Life Sciences Ltd., Cambridgeshire, England; ISK #: 268/023923; 11/18/02). TFNG Technical (N-(4-trifluoromethylnicotinoyl) glycine; 99.4% pure) was used *in vitro* on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA^{-} at 0 (DMSO), 33, 100, 333, 1000, 2500, and 5000 ug/plate (triplicate plates) to test mutagenicity. A rangefinding study (pour plate method) was performed on each strain of *S. typhimurium* and *E. coli* at 5, 15, 50, 150, 500, 1500 and 5000 ug/plate (triplicate cultures). Subsequently all strains were tested at 0 (DMSO), 50, 150, 500, 1500 and 5000 ug/plate (triplicate plates, with pre-incubation for 30 minutes) both with and without metabolic activation (S9) for 72 hours. Results of the rangefinding test showed no substantial increases in revertant colonies occurred with any tester strain after exposure to TFNG (+ or - S9). There were also no treatment-related increases in revertant colony numbers with the subsequent pre-incubation experiment. No adverse effect. Acceptable. Silva, 4/12/05

**52964-0016 208805 Matsumoto, K., "IKI-220 Technical: reverse mutation test with amendment" Institute of Environmental Toxicology, Ibaraki, Japan, 1/23/02. Laboratory Project ID: IET 00-0147. Standard reverse mutation test strains (TA 1535, TA 100, TA 1537, TA 98, WP2 uvrA) were exposed to flonicamid (98.7% purity) at levels up to 5 mg/plate (a level which did not elicit toxicity and which was soluble in the test system) with 20-minute pre-incubation step in standard Ames-style assays with and without S-9 in each test. There were three reps per dose level in two independent tests. All

strains and all exposure levels were negative with and without S-9. Positive controls were functional. Study is acceptable, with no adverse effects. Aldous, June 4, 2004.

**52964-0017 208806 Matsumoto, K., "IKI-220 Technical: *in vitro* mouse lymphoma gene mutation test, " Institute of Environmental Toxicology, Ibaraki, Japan, 1/23/02. Laboratory Project ID: IET 00-0150. Mouse lymphoma L5178Y $TK^{+/-}$ cells of clone 3.7.2.C were exposed to Flonicamid (IKI-220 Technical), Lot No. 9809, purity 98.7%, at concentrations up to 2290 μg/ml (10 mM) for 3 hr, followed by a 48-hr expression period. Aliquots were dispensed into microwell trays and incubated for 12 days in the presence of trifluorothymidine prior to counting. Investigators assessed survival at the beginning and end of the expression period, growth in cell numbers during that period, and mutant frequency at the end of the incubation period (including distinguishing between large and small colonies). There were duplicate cultures, with three microtiter plates per culture at every dose level, in each of two separate experiments, employing 3-fold and 2-fold step dilutions of 2290 μg/ml, respectively. Positive controls, cyclophosphamide and methyl methanesulfonate (with and without S-9) were used in each experiment, and were functional. Acceptable, with no adverse effects. Aldous, March 2, 2004.

CHROMOSOME EFFECTS

**52964-0018 208807 Matsumoto, K., "IKI-220 Technical: in vitro cytogenetics test with amendment," Institute of Environmental Toxicology, Ibaraki, Japan, 1/23/02. Laboratory Project ID: IET 00-0149. Flonicamid (IKI-220 Technical), 98.7% purity, was tested in a Chinese hamster lung cell line in an *in vitro* cytogenetics test. The preliminary growth inhibition test showed that the limit test standard of 2290 μg/ml (10 mM) was tolerated (at least 72% of control growth in the growth inhibition test), and there was no precipitation at that dose. Dose levels in all tests were 0, 573, 1145, and 2290 μg/ml. There were duplicate cultures at each dose level in each of two experiments, with 100 cells evaluated per culture. Positive controls, Mitomycin C (0.1 μg/ml) and benzo(a)pyrene (40 μg/ml) were used without and with S-9, respectively. Experiment 1 involved a 6 hr exposure to test article (with and without S-9), with 18 hr subsequent culturing in fresh medium. Experiment 2 did not use S-9, but exposure periods were 24 hr and 48 hr. Metaphase arrest was accomplished by colcemid, 0.2 μg/ml, 2 hr before harvest. All cytogenetics tests for flonicamid were negative, and positive controls were highly effective. Acceptable, with no adverse effects. Aldous, 3/3/04.

DNA DAMAGE

** 52964-0084 216058 "IKI-220 Technical: *in vivo* DNA Repair (UDS) Test Using Rat Hepatocytes," (Mehmood, Z.; Huntingdon Life Sciences Ltd., Cambridgeshire, England; Document #: ISK 269/032007; 1/14/03). Flonicamid technical (IKI-220; 98.7% pure) was administered by gavage to Sprague-Dawley male rats (5/dose/time-point) in a single dose at 0 (1% w/v methylcellulose), 600 and 2000 mg/kg (limit test). Animals were subsequently terminated at 2 and 14 hours post-dosing and hepatocytes were assessed by autoradiography for unscheduled DNA synthesis (150 cells from 3 slides were scored/animal). The IKI-220 did not cause any significant increase in the nuclear grain count at any dose and therefore does not cause DNA damage in the rat liver in this system. Positive controls were highly effective. Acceptable, with no adverse effects. Silva, 4/15/05.

**52964-0019 208808 Matsumoto, K., "IKI-220 Technical: micronucleus test in mice with amendment," Institute of Environmental Toxicology, Ibaraki, Japan, 1/23/02. Laboratory Project ID: IET 00-0148. Five (SPF) ICR (Crj:CD-1) mice/sex were dosed twice at 24 hr intervals by gavage in 0.5% CMC with 0, 250, 500, or 1000 mg/kg/day flonicamid (M) or 0, 125, 250, or 500 mg/kg/day flonicamid (F). Mice were sacrificed 24 after the second treatment. Positive controls received Mitomycin C: 10 mg/kg/day, in a single administration 24 hr before sacrifice. Selected flonicamid dose levels were based on mortalities and/or severe clinical signs at higher dose levels in a toxicity study. There were no clinical signs at the doses tested in the definitive study. Treatment did not elicit

increased micronuclei, nor was there any change in PCE/(NCE + PCE) ratios. Positive controls were functional. Study is acceptable, with no adverse effects. Aldous, June 4, 2004.

52964-0083 216057 *"In Vivo* Comet Assay with Technical Flonicamid," (Sasaki, Y.F.; Laboratory of Genotoxicity, Hachinohe National College of Technology, Aomori, Japan; ISK/AN-2106; 12/10/02). Flonicamid technical (98.7% pure) was administered by gavage at 0 (0.5% CMC-Na), 375, 750 and 1500 mg/kg to male ddY mice (4/dose/time point). Animals were terminated at 3 and 24 hours and their colon, liver and lungs were examined for DNA damage in a "comet" assay that examines migration of DNA after electrophoresis at alkaline pH. DNA was visualized with ethidium bromide. No death, morbidity or clinical signs were observed in any of the mice following treatment with flonicamid. The induction of DNA damage was evaluated by increase in DNA migration. The positive controls functioned as predicted. No adverse effect. This is not a FIFRA Guideline study, however it provides useful information. Silva, 4/15/05

NEUROTOXICITY (RAT)

Rangefinding study:

52964 - 0086 216060 "A 28-Day Neurotoxicity Range-Finding Study of IKI-220 Technical in Rats," (Schaefer, G.J.; WIL Research Laboratories, Inc., Ashland, OH; Document #: WIL-449001; 1/13/03). IKI-220 technical (100% pure) was fed in diet to Crl:CD® (SD)IGS BR rats at 0 (diet), 200, 500, 1000, 5000, 10000 (5 rats/sex/dose; 17, 41, 84, 388 & 712 mg/kg/day for males; 18, 46, 84, 429 & 807 mg/kg/day for females) and 20000 ppm (5 females only;1012 mg/kg/day) for 28 days. NOEL = 1000 ppm (84 mg/kg/day, males) and 5000 ppm (429 mg/kg/day, females) (A single female was found dead at 20000 ppm after showing hunched appearance (all females, study days 14 - 28), decreased defecation (generally throughout the study beginning study day 2) and paleness (days 10, 21 and 28). Mean body weight losses and decreased food consumption in males at $\geq$ 5000 ppm (388 mg/kg/day) and in females at $\geq$ 10000 ppm (807 mg/kg/day). All animals were necropsied but no microscopic examinations were performed. No adverse effect indicated. These data are supplemental. (Silva, 4/11/05)

Definitive studies:

52964 - 0085 216059 "An Acute Neurotoxicity Study in Rats with IKI-220 Technical–Amended Report," (Ridder, W.E., Watson, M.; Toxicology and Pharmacology, Ricerca Biosciences, LLC, Painsville, OH; Document #: 012076-1-2; 12/18/02). IKI-220 technical (98.7% pure) was administered in a single oral gavage dose to Crl:CD® (SD)IGS BR® rats at 0 (0.5% methylcellulose aqueous), 100, 300, (10/sex/dose), 600 (5 males) and 1000 mg/kg (5 males–satellite group; 10 females). Neurobehavioral assessment included a functional observational battery (FOB) and a motor activity test that were performed on all animals at approximately the same time of day, before initiation of treatment, approximately 30-60 minutes after dosing and 7 and 14 days post-dosing. Neurobehavioral assessment included a functional observational battery and a motor activity test performed on all animals. Systemic NOEL = 600 mg/kg (A male at 1000 mg/kg was found dead after showing decreased activity, impaired locomotion and tremors during open field evaluation at 30/60 minutes post dosing. A female at 1000 mg/kg had abnormal scores showing impaired mobility, tremors and other gait abnormalities during neurological evaluation at 30/60 minutes post dosing. There was a trend (Bartlett's test) to decreased mean absolute and relative food consumption in females although the decrease was only 5% at 1000 mg/kg after 1 and 2 weeks. Males on the other hand showed a trend to increased relative food consumption at week 2. Neurological NOEL = 600 mg/kg (There was a treatment-related increase in landing foot spread at 1000 mg/kg in both sexes at 30-60 min. LD50 for males was shown to be 884 mg/kg and 1768 mg/kg for females. In general males showed increased palpebral closure (30-60 min), fur appearance (day 14) and salivation (30/60 min) at 1000 mg/kg. Males at 1000 mg/kg showed increased involuntary movement, abnormal gait, arousals and bizarre behavior, primarily at 30/60 mins. Females at 1000 mg/kg showed increased effects on mobility, posture and involuntary movement at 30/60 mins. Both sexes at 1000 mg/kg showed increased effects on total rears, supported rears, unsupported rears, defecation and urination

primarily at 1000 mg/kg (both sexes). There were increases in righting reflex, hindlimb strength, auditory response and touch response in males at 1000 mg/kg. In females, tail pinch, and touch response were very slightly increased at 1000 mg/kg. Males at 1000 mg/kg had decreased mean distance traveled, and increased mean resting time (30/60 min).) No adverse effect. No treatment-related microscopic changes were noted in the tissues examined. Not acceptable but upgradeable with appropriate positive control studies. (Silva, 4/19/05)

** 52964 - 0087 216061 "A Dietary Subchronic (90-Day) Neurotoxicity Study of IKI-220 Technical in Rats," (Schaefer, G.J.; WIL Research Laboratories, Inc., Ashland, OH; Document #: WIL-449002; 1/21/03). IKI-220 technical (98.7% pure) was fed in diet to Crl:CD® (SD)IGS BR rats (10/sex/dose) for 13 weeks at 0 (diet), 200, 1000 and 10000 ppm (approximately 0, 13, 67 and 625 mg/kg/day–M; 0, 16, 81 and 722 mg/kg/day–F). An FOB and locomotor activity (60 min) were evaluated pretest and weeks 3, 7 and 12. At week 13, selected tissues were examined microscopically. NOEL = 1000 ppm (There was an increased incidence in dried red material around nose in both sexes at 10000 ppm. There was a statistically significant decrease in body weight, body weight gain and food consumption in both sexes at 10000 ppm.) Neurological NOEL = 200 ppm (There was a statistically significant decrease in rearing scores in males at $\geq$ 1000 ppm throughout the study (within historical control ranges). Males at week 12 showed a statistically significant increase in Hindlimb Footsplay at 10000 ppm. Test related Physiological Observations were observed as decreased body weight in both sexes at 10000 ppm. Males showed a statistically significant decrease in total and ambulatory counts at week 7 at 10000 ppm (both below Historical Controls). Females had statistically significantly decreased mean ambulatory motor activity at study week 3.) The author considered the neurotoxicity NOEL to be 10,000 ppm based on variability of responses. No adverse effect. Acceptable. (Silva, 4/20/05)

SUBCHRONIC STUDIES

Rat 90-Day Dietary Toxicity Study

52964-0012 208801; " IKI-220 Technical:90-Day Subchronic Oral Toxicity Study in Rats"; (M. Kuwahara; The Institute of Environmental Toxicology, Ibaraki 303-0043, Japan; Report No. IET 98-0141; 2/19/02); Twelve Wistar rats/sex/group received 0, 200, 500 or 1000 ppm of IKI-220 Technical (lot no. 9809, purity: 98.7%) in the diet for 13 weeks. Twelve males/group also received 50 or 2000 ppm in the diet and an additional group of 12 females received 5000 ppm of the test material in the diet for the same time period ((M) 0, 3.08, 12.1, 60.0, 119.4 mg/kg/day, (F) 0, 14.5, 72.3, 340 mg/kg/day). No deaths resulted from the treatment. There were no apparent treatment-related clinical signs or effects noted in the functional observational battery or motor activity evaluation. The mean body weights and body weight gain for the 2000 ppm males and 5000 ppm females were lower than those of the control groups over the course of the study (NS). The mean food consumption was reduced for the 5000 ppm females ($p<0.01$ or 0.05). The mean hematocrit value for the 5000 ppm females was lower than that of the control ($p<0.05$). The mean MCHC value for these females was greater than that of the control ($p<0.05$). In the clinical chemistry evaluation, the mean triglyceride concentration was lower for both the 2000 ppm males and the 5000 pm females ($p<0.01$ or 0.05). The mean absolute and relative liver weights for the 5000 ppm females was greater than those values for the control ($p<0.01$). The mean absolute and relative kidney weights for the 1000 and 2000 ppm males and for the 5000 ppm females were greater than those values for the control ($p<0.01$ or 0.05). In the histopathology examination, centrilobular hepatocellular hypertrophy was noted in the livers of the 2000 ppm males and the 5000 ppm females ((M), 0: 0/12 vs. 2000: 12/12; (F), 0: 0/12 vs. 5000: 12/12). Deposition of hyaline droplets in the proximal tubules of the kidney was noted for the males in the 200 ppm group and above (0: 0/12 vs. 200: 8/12, 1000: 12/12 and 2000: 12/12). In addition, tubular basophilic change in the kidney was evident for the 1000 and 2000 ppm males (0: 0/12 vs. 1000: 11/12, 2000: 12/12) and granulated casts were identified in dilated tubules of these same males (0: 0/12 vs. 1000: 5/12, 2000: 12/12). The females of the 5000 ppm group demonstrated cytoplasmic vacuolation in the proximal tubules of the kidney (0: 0/12 vs. 5000: 12/12). **No adverse effects were evident.** Target organs: liver and kidney. **Subchronic NOEL:** (M) 50 ppm (3.08 mg/kg/day) (based upon the incidence of hyaline droplet deposition in the kidneys of the 200 ppm males), (F) 1000 ppm (72.3 mg/kg/day) (based upon the increased kidney weight and the accompanying vacuolation in the

proximal tubules of the kidney in the 5000 ppm treatment group). **Study acceptable.** (Moore, 5/11/04)

Rat 28-Day Dietary Toxicity Study

52964-0011 208800; "IKI-220 Technical: 28-Day Dose Range Finding Study in Rats"; (M. Kuwahara; The Institute of Environmental Toxicology, Ibaraki 303-0043, Japan; Report No. IET 98-0140; 2/19/02); Six Wistar (Jcl:Wistar) rats/sex/group received 0, 100, 500, 1000, and 5000 ppm of IKI-220 Technical (lot no. 9809; purity: 98.7%) in the diet for 28 days. Additional male and female groups of 6 animals received 50 ppm (males) or 10000 ppm (females) in the diet over the same time period ((M) 0, 3.61, 7.47, 36.5, 73.8, 353.4 mg/kg/day, (F) 0, 8.36, 41.2, 81.9, 372.6, 642 mg/kg/day). No deaths resulted from the treatment. The mean body weights of the 5000 ppm males and the 10000 ppm females were lower than those of the controls with a significant effect noted during the first 2 to 3 weeks of treatment. Mean food consumption was lower as well for the animals in these groups. In the hematology evaluation, the 5000 ppm males demonstrated lower mean hematocrit and red blood cell count than those values of the control group ($p<0.05$). In the clinical chemistry evaluation, the mean cholesterol levels were increased for both sexes in the 5000 ppm group and for the 10000 ppm females ($p<0.05$ or 0.01). The mean triglyceride concentrations for the males in the 5000 ppm group and for the females in the 10000 ppm group were lower than those of the controls (males, NS; females, $p<0.01$). The mean absolute and relative liver weights for both sexes in the 5000 ppm group and for the 10000 ppm females were greater than those of the controls ($p<0.05$ or $p<0.01$). The mean absolute and relative kidney weights for the males in the 5000 ppm groups were greater than those of the controls ($p<0.05$ or $p<0.01$). The mean relative spleen weights for the 10000 ppm females were greater than that of the controls ($p<0.01$). The mean absolute and relative adrenal weights were lower for the 10000 ppm females than for the controls ($p<0.05$ or $p<0.01$). In the microscopic examination, centrilobular hepatocellular hypertrophy in the liver was noted for both sexes in the 5000 ppm group and for the 10000 ppm females ((M) 0: 0/6 vs. 5000: 6/6, (F) 0: 0/6 vs. 5000: 4/6, 10000: 6/6). For the 100 ppm males and above, there was increased deposition of hyaline droplets in the proximal tubules of the kidneys (0: 0/6 vs. 100: 3/6, 500 and above: 6/6). Target organs: liver and kidneys (males only). **No adverse effect indicated. Subacute NOEL:** (M) 50 ppm (3.61 mg/kg/day) (based upon the incidence of increased hyaline droplet deposition in the kidneys of the 100 ppm males), (F) 1000 ppm (81.9 mg/kg/day) (based upon the increased absolute and relative liver weight and centrilobular hepatocellular hypertrophy in the liver of the 5000 ppm females). The immunostaining of the kidneys of the 5000 ppm satellite males with an antibody against alpha2u-globulin revealed an increased presence of this protein in the male kidneys. **Study supplemental.** (study was performed for the purposes of dose range-finding). (Moore, 5/10/04)

Rat Repeated Dosing 28-Day Dermal Toxicity Study

52964-0014 208803; "A 28-Day Repeated Dose Dermal Toxicity Study in Rats with IKI-220 Technical"; (W. Ridder; Toxicology and Pharmacology, Ricerca LLC, Painesville, OH; Report No. 012074-1; 11/28/01); The skin of ten Crl:CD (SD) (IGS) BR rats/sex/group was exposed to 0, 20, 150 or 1000 mg/kg/day of IKI-220 Technical (lot no. 9809, purity: 98.7%) for 6 hours/day, 7 days/week for 4 weeks. The test material was suspended in distilled water and the site of application was covered by a semi-occlusive wrap. No deaths resulted from the treatment. No dermal irritation or other clinical signs were evident. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related effects were noted in the hematology or clinical chemistry evaluations. In the necropsy and histopathological examinations, no treatment-related lesions were evident and the organ weights were not affected by the treatment. **No adverse effect indicated. Dermal Subchronic NOEL (both local and systemic):** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 5/13/04)

Mouse 90-Day Dietary Toxicity Study

52964-0010 208799; "A 13-Week Feeding Study in Mice with IKI-220 Technical"; (W.E. Ridder, M. Yoshida, M. Watson; Toxicology & Metabolism, Ricera, LLC, Painesville, OH; Report No. 8090-1; 12/11/01); Ten Crl:CD-1 (ICR) BR mice/sex/group received 0, 100, 1000 or 7000 ppm of IKI-220 Technical (lot no. 9809, purity: 98.7%) in the diet for 13 weeks ((M) 0, 15.3, 153.9, 1069 mg/kg/day, (F) 20.1, 191.5, 1248 mg/kg/day). No treatment-related deaths occurred during the study. Both sexes in the 7000 ppm treatment group exhibited lower body weight gain over the course of the study (NS). In the hematology analysis, both sexes in the 7000 ppm group had lower mean rbc counts, hemoglobin concentrations, and hematocrits ($p<0.01$ or 0.05). The mean corpuscular volume, mean corpuscular hemoglobin and percentage of reticulocytes were increased for both sexes in this group ($p<0.01$). These high dose animals were suffering from a mild macrocytic anemia. In the clinical chemistry examination, both sexes in the 7000 ppm group exhibited increased mean concentrations of total bilirubin ((M) $p<0.01$, (F) NS), serum glucose ((M) NS, (F) $p<0.01$), and sodium and chloride levels ((M) $p<0.01$, (F) NS). The mean potassium levels for this group were lower ((M) $p<0.05$, (F) NS). The mean absolute liver weight for the 7000 ppm males and the mean absolute spleen weight for both sexes in the 7000 ppm group were greater than those of the control ($p<0.01$). The mean relative liver and spleen weights for both sexes in the 7000 ppm group were greater than those of the control ($p<0.01$). In the histopathological examination, hypocellularity and increased pigment deposition were noted in the bone marrow of both sexes in the 7000 ppm group (hypocellularity, (M) 0:0/10 vs. 7000: 8/10, (F) 0: 0/10 vs. 7000: 6/10), (pigment deposition, (M) 0: 0/10 vs. 7000: 7/10, (F) 0: 0/10 vs. 5/10). In the liver, centrilobular hepatocellular hypertrophy was noted for both sexes in the 7000 ppm group and for the males in the 1000 ppm group ((M) 0: 0/10 vs. 1000: 3/10, 7000: 10/10, (F) 0: 0/10 vs. 7000: 10/10). In the spleen, there was an increased incidence of extramedullary hematopoiesis in both sexes of the 1000 and 7000 ppm treatment groups ((M) 0: 2/10 vs. 1000: 5/10, 7000: 10/10, (F) 0: 3/10 vs. 1000: 7/10, 7000: 10/10). In addition, there was increased pigment deposition in the spleen for both sexes in the 7000 ppm group ((M) 0: 0/10 vs. 7000: 8/10, (F) 0: 0/10 vs. 7000: 10/10). **Possible adverse effect:** anemia; **Subchronic NOEL:** (M/F) 100 ppm (M: 15.3, F: 20.1 mg/kg/day) (based upon the incidence of centrilobular hypertrophy in the liver and increased pigment deposition in the spleen of the1000 ppm treatment group); **Study supplemental** (protocol did not include all of the parameters set forth in the 870.3100 guidelines). (Moore, 5/7/04)

RAT METABOLISM

52964-0020 208809 Neal, T. R., and M. C. Savides, "Pilot study of the routes of elimination and pharmacokinetics of [^{14}C]IKI-220 in rats," Ricerca, LLC, Painesville, OH, 6/29/01. Ricerca Document No. 10001-1. Five CRL:CD®(SD)IGS BR® rats/sex/level were dosed by gavage in 0.75% methylcellulose suspension with single administrations of either low or high doses of flonicamid. Intended dose levels were 2 and 50 mg/kg for both the pilot excretion study and for the pilot pharmacokinetics study. By error, the actual mean administered doses for the pilot excretion study were 0.85 and 21 mg/kg, which was unlikely to have affected results. The pilot excretion study assessed exhaled CO_2 as well as urine, cage washings, and feces at intervals of 24 hr or less for 7 days. No measurable CO_2 was detected in exhaled air. Urine plus cage wash samples accounted for 89–92% of administered label. About 5-6% of administered label was found in feces. Only 2-3% of label resided in carcasses at day 7. Half-life of administered flonicamid was 5 to 6 hr. T_{max} was estimated to be 0.3 to 0.6 hr. There was no apparent sex difference in disposition, nor was there any apparent difference due to dose level. This is a useful supplementary study, suitable for setting parameters for a definitive study to be directed at evaluating tissue distribution and metabolite characterization. Aldous, 2/24/04.

52964-0088 215998 Pharmacokinetics of an Oral Dose of [^{14}C]IKI-220 in Sprague-Dawley Rats," (Neal, T. R., and M. C. Savides, Metabolism Division, Ricerca, LLC, Painesville, OH, Ricerca Document # 10002-1; 9/27/01). [^{14}C]IKI-220 (radiolabelled = 98.5% pure; unlabelled = 99.7%) was administered by gavage to CRL:CD®(SD)IGS BR® rats at 0 (0.75% methylcellulose suspension, 1/sex), 2 and 400 mg/kg (5/sex/dose). Blood samples were taken at 0, 10, 20 and 40 minutes and at 1, 2, 3, 4, 8, 24, 48 and 72 hours (terminated at 72 hours) to determine pharmacokinetics. After treatment, IKI-220 was rapidly absorbed and peak plasma radioconcentrations were rapidly achieved. Pharmacokinetics at 2 mg/kg were similar between the sexes but were different at 400 mg/kg.

Females had a half-life of 6.8 hours after 400 mg/kg treatment. This was similar to the 4.5 hour half-life after treatment with 2 mg/kg. The average half-life in males at 2 mg/kg was 5.2 hours (similar to females), however at 400 mg/kg the plasma concentrations reached a plateau that lasted several hours (average half-life = 11.6 hours) in males and was statistically significantly different than high dose females and low dose males. Data are supplemental. Silva, 4/25/05.

52964-0089 215999 "Metabolism of [^{14}C]IKI-220 in Rats," (Gupta, K.S., Shah, J.F., McClanahan, R.H.; Metabolism Division, Ricerca, LLC, Painesville, OH, Ricerca Document # 010052-1; 7/15/02). [^{14}C]IKI-220 (radiolabelled = 98.5% pure; unlabelled = 99.7%) was used in 3 experiments in order to characterize metabolism in CRL:CD®(SD)IGS BR® rats: Study #13364 (Biliary): 4 rats/sex/dose were administered a single oral gavage dose of [^{14}C]IKI-220 at 2 or 400 mg/kg, then terminated at 48 hours. Study #10005 (Single-Dose Excretion): 3 or 5/sex/dose/timepoint were treated with a single oral gavage dose of [^{14}C]IKI-220 at 2 or 400 mg/kg and terminated at 0.5, 6, 24 and 168 hours (2 mg/kg) or 3 (M), 1 (F), 14.5 (M), 8 (F), 24 and 168 hours. Study #10007 (Multi-Dose Excretion): 2/sex/dose/timepoint were treated with 14 consecutive oral gavage doses of [^{12}C]IKI-220 at 2 mg/kg, then one dose of [^{14}C]IKI-220 on the 15th day before termination at 0.5, 6, 24 and 168 hours following [^{14}C]IKI-220 administration. The negative control and vehicle was 0.75% methylcellulose/HPLC Grade H_2O. Livers were collected and analyzed for metabolites in 10005 and 10007. Excretion of IKI-220 and metabolites occurred primarily in the urine and to a lesser extent in the feces. It was metabolized by several routes, including nitrile hydrolysis, amide hydrolysis, N-oxidation and hydroxylation of the pyridine ring. Combinations of pathways occurred, leading to the formation of multiple metabolites. Proposed metabolic pathways are shown of page 29 of the report. The data in this study comprise the metabolic pathway determination of a complete metabolism study. This section is acceptable. No adverse effect. Silva, 4/26/05.

52964-0090 216000 "Study of the Elimination and Distribution of Radiolabel Following a Single Oral Administration of [^{14}C]IKI-220 to Sprague-Dawley Rats," (Neal, T.R., Savides, M.C., Dow, P.; Toxicology and Pharmacology, Ricerca, LLC, Painesville, OH, Ricerca Document # 10005-1; 4/19/02). [^{14}C]IKI-220 (radiolabelled = 98.5% pure; unlabelled = 99.7%) was administered by oral gavage to CRL:CD®(SD)IGS BR® rats at 0 (0.75% methylcellulose/HPLC Grade H_2O; 1/sex/dose at 6 and 168 hr termination), 2 mg/kg (3/sex/timepoint at 0.5, 6, 24 hours and 5/sex at 168 hour termination) and 400 mg/kg (3/sex/timepoint at 0.5, 6, 24 hours and 5/sex at 168 hour termination) to determine elimination and distribution. At 2 and 400 mg/kg, [^{14}C]IKI-220 radioactivity was rapidly absorbed and excreted. A quantitative recovery was achieved during the 168 hour collection period. Urine contained 90% (including cage wash) of administered radioactivity, the majority of which was obtained within 24 hours of dosing at 2 mg/kg and by 48 hours at 400 mg/kg. Fecal elimination at 2 and 400 mg/kg was 5% of administered dose. In tissues, radioactivity levels increased rapidly with maximum concentrations mirroring those observed in the blood. While radioactivity was observed at all early timepoints in tissues, by 168 hours the levels had (where detectable) decreased by 50 - 100 fold. By 168 hours the carcasses contained 2% of radioactivity and liver had the highest tissue content (< 0.15%). At 2 mg/kg the greatest concentrations of radioactivity at 0.5 hours post dose for males and females respectively in liver (2.54-2.50 ug eq/g), kidney (2.35-2.67 ug eq/g), adrenals (5.07-6.52 ug eq/g), thyroid (4.02-4.26 ug eq/g) and ovaries (females - 3.77 ug eq/g). At 400 mg/kg males had the greatest concentration of radiolabel at 3 hours post dose in the liver (442 ug eq/g), kidney (311 ug eq/g), adrenals (672 ug eq/g) and thyroid (652 ug eq/g). Females had the greatest radiolabel concentrations at 1 hour post dose for liver (325 ug eq/g), kidney (359 ug eq/g), adrenals (689 ug eq/g) and thyroid (782 ug eq/g). Blood concentrations in both sexes correlated with those at the corresponding time points and dose level in the pharmacokinetic study. Supplemental data. No adverse effect. Silva, 4/27/05

52964-0091 216001 "Study of the Elimination and Distribution of Radiolabel Following Multiple Oral Administrations of [^{12}C/ ^{14}C]IKI-220 to Sprague-Dawley Rats," (Neal, T.R., Savides, M.C., Dow, P.; Toxicology and Pharmacology, Ricerca, LLC, Painesville, OH, Ricerca Document # 10007-1; 4/19/02). [^{12}C/^{14}C]IKI-220 (radiolabelled = 98.5% pure; unlabelled = 99.7%) was administered by oral gavage to CRL:CD®(SD)IGS BR® rats at 0 (0.75% methylcellulose/HPLC Grade H_2O; 1/sex/dose at 6 and 168 hr termination), and 2 mg/kg (3/sex/timepoint at 0.5, 6, 24 hours and 5/sex at 168 hour termination) for 14 consecutive days, followed by a single treatment of [^{14}C]IKI-220 on the 15th day. Samples were

taken at the prescribed time points that began following the final treatment. At 2 mg/kg, [^{12}C/^{14}C]IKI-220 radioactivity was rapidly absorbed and excreted. A quantitative recovery was achieved during the 168 hour collection period. Urine contained 90% (including cage wash) of administered radioactivity, the majority of which was obtained within 24 hours of dosing and fecal elimination at 2 mg/kg was 7% of administered dose. In tissues, radioactivity levels increased rapidly with maximum concentrations mirroring those observed in the blood. While radioactivity was observed at all early timepoints in tissues, by 168 hours the levels had (where detectable) decreased by 100 fold. By 168 hours the carcasses contained 2% of radioactivity and liver had the highest tissue content (< 0.12%). At 2 mg/kg the greatest concentrations of radioactivity at 0.5 hours post dose for males and females respectively in liver (2.39-2.51 ug eq/g), kidney (2.55-2.54 ug eq/g), adrenals (2.54-2.41 ug eq/g), thyroid (2.69-3.49 ug eq/g) and ovaries (females - 2.71 ug eq/g). Blood concentrations in both sexes correlated with those at the corresponding time points and dose level in the pharmacokinetic study. Repeat dosing of IKI-220 had no effect on the disposition of radioactivity when compared to a single dose at the same dose level in rat. was rapidly absorbed and excreted. Supplemental data. No adverse effect. Silva, 4/27/05

52964-0092 216002 "Study of the Biliary Elimination of Radiolabel Following Oral Administration of [^{14}C]IKI-220 to Sprague-Dawley Rats," (Dow, P.; Toxicology and Pharmacology, Ricerca, LLC, Painesville, OH, Ricerca Document # 13364-1; 4/19/02). [^{14}C]IKI-220 (radiolabelled = 98.5% pure; unlabelled = 99.7%) was administered by oral gavage to CRL:CD®(SD)IGS BR® rats at 0 (0.75% methylcellulose/HPLC Grade H_2O; 1/sex/dose), 2 and 400 mg/kg (4/sex/dose), followed by a 48 hour termination time. At 2 and 400 mg/kg, [^{14}C]IKI-220 radioactivity was rapidly absorbed and excreted. A quantitative recovery was achieved during the 48 hour collection period. Urine contained 85% (including cage wash) of administered radioactivity at 2 mg/kg and 80% at 400 mg/kg, the majority of which was excreted within 24 hours of dosing. Biliary excretion was low (4% at 2 mg/kg and 5% at 400 mg/kg) and the majority of radiolabel was excreted within the first 24 hours. Low levels of radioactivity were in feces (3.5-5.0%) and carcass (2.0-3.2%) at 2 mg/kg and in feces (3.8%) and carcass (1.5-2.1%). Therefore, biliary excretion was not a significant route of elimination of radioactivity. Increasing dose level had little effect on the disposition of radioactivity and there was no accumulation of radioactivity in the residual carcass. No sex-related differences were observed in any of the parameters measured. Supplemental data. No adverse effect. Silva, 4/27/05

CONCLUSION: Although none of the metabolism studies reviewed by DPR are acceptable alone, the combination of studies 52964-0089 to 0092/215999 to 216002 provided sufficient data to have a complete metabolism study. Silva, 4/27/05.

SUPPLEMENTAL INFORMATION

Acute Studies Performed with Metabolites of Flonicamid:

** 52964 - 053 216027 "TFNA: Acute Oral Toxicity Study in Rats," (Damme, B.; RCC Ltd, Toxicology Division, Itingen, Switzerland; Document #: 834142; 2/7/02). TFNA (99.4% pure) was administered by a single oral gavage to HanBrl: Wist (SPF) rats (3/sex/dose) at 2000 mg/kg after being fasted for 16 to 20 hours. Animals were subsequently observed for 14 days post-dosing. There were no deaths, no clinical signs, no effects on body weights and no macroscopic findings. There were no treatment-related effects in either sex. LD_{50} > 2000 mg/kg; Toxic Category III This study is acceptable. No adverse effects indicated. Silva, 2/4/05

** 52964 - 054 216028 "TFNA-AM: Acute Oral Toxicity Study in Rats," (Damme, B.; RCC Ltd, Toxicology Division, Itingen, Switzerland; Document #: 834750; 2/7/02). TFNA-AM (100% pure) was administered by a single oral gavage to HanBrl: Wist (SPF) rats (3/sex/dose) at 2000 mg/kg after being fasted for 16 to 20 hours. Animals were subsequently observed for 14 days post-dosing. There were no deaths, no clinical signs, no effects on body weights and no macroscopic findings. There were no treatment-related effects in either sex. LD_{50} > 2000 mg/kg; Toxic Category III This study is acceptable. No adverse effects indicated. Silva, 2/4/05

** 52964 - 055 216029 "TFNG: Acute Oral Toxicity Study in Rats," (Damme, B.; RCC Ltd, Toxicology Division, Itingen, Switzerland; Document #: 834761; 2/7/02). TFNG (99.4% pure) was administered by a single oral gavage to HanBrl: Wist (SPF) rats (3/sex/dose) at 2000 mg/kg after being fasted for 16 to 20 hours. Animals were subsequently observed for 14 days post-dosing. There were no deaths, no clinical signs, no effects on body weights and no macroscopic findings. There were no treatment-related effects in either sex. LD_{50} > 2000 mg/kg; Toxic Category III This study is acceptable. No adverse effects indicated. Silva, 2/4/05

** 52964 - 056 216030 "TFNG-AM: Acute Oral Toxicity Study in Rats," (Damme, B.; RCC Ltd, Toxicology Division, Itingen, Switzerland; Document #: 834772; 2/7/02). TFNG-AM (99.5% pure) was administered by a single oral gavage to HanBrl: Wist (SPF) rats (3/sex/dose) at 2000 mg/kg after being fasted for 16 to 20 hours. Animals were subsequently observed for 14 days post-dosing. There were no deaths, no clinical signs, no effects on body weights and no macroscopic findings. There were no treatment-related effects in either sex. LD_{50} > 2000 mg/kg; Toxic Category III This study is acceptable. No adverse effects indicated. Silva, 2/4/05

** 52964 - 057 216031 "TFNA-OH: Acute Oral Toxicity Study in Rats," (Damme, B.; RCC Ltd, Toxicology Division, Itingen, Switzerland; Document #: 834783; 2/7/02). TFNA-OH (100% pure) was administered by a single oral gavage to HanBrl: Wist (SPF) rats (3/sex/dose) at 2000 mg/kg after being fasted for 16 to 20 hours. Animals were subsequently observed for 14 days post-dosing. There were no deaths, no clinical signs, no effects on body weights and no macroscopic findings. There were no treatment-related effects in either sex. LD_{50} > 2000 mg/kg; Toxic Category III This study is acceptable. No adverse effects indicated. Silva, 2/7/05

Additional Data and Discussions:

52964 - 051 216025 "Mammalian and Genetic Toxicology Overview of Flonicamid Technical (Update)," (McCarty, J.D.; FMC Corporation, Agricultural Products Group, Princeton, NJ; Document #: IB-2002-MB-003-01, 1/20/03). This report contains a complete discussion of the acute, subchronic, chronic, reproduction, developmental, neuro- and genetic toxicology and metabolism of flonicamid. This contains information similar to the Product Registration Recommendation Sheet and the Summary of Toxicology Data put forth by DPR. All studies discussed in this report were presented to and reviewed by DPR. The results of the DPR reviews are presented in worksheets and summarized in the Product Registration Recommendation Sheet and the Summary of Toxicology Data. This information is supplemental. No worksheet was performed for this data volume. Silva, 2/2/05.

52964 - 052 216026 "Supplement to Mammalian and Genetic Toxicology Overview of Flonicamid Technical (Update)," (McCarty, J.D.; FMC Corporation, Agricultural Products Group, Princeton, NJ; Document #: IB-2004-MB-002-01, 4/1/04). This report contains a supplemental discussion of the additional data on the oncogenicity of flonicamid technical. It was stated that after the initial mouse oncogenicity study, a second 18-month mouse oncogenicity study was conducted to determine a definitive oncogenicity NOEL. The latter study confirmed a non-linear threshold response for lung tumors in CD-1 mice. This volume contained, in addition, a comparison of all the effects observed in the subchronic and chronic studies performed in rat, mouse and dog (also reviewed by DPR). The results of the DPR reviews are presented in worksheets and summarized in the Product Registration Recommendation Sheet and the Summary of Toxicology Data. This information is supplemental. No worksheet was performed for this data volume. Silva, 2/2/05.

52964 - 058 216032 "Waiver Request for a 28-Day Inhalation Toxicity Study on Flonicamid Technical," (Li, K.L.; FMC Corporation, Agricultural Products Group, Princeton, NJ; Document #: IB-2002-MB-001-01; 1/16/03) This document contains a request that the requirement for a 28-day inhalation toxicity study in rats be waived. This is based on HED Standard Operating Procedure entitled "Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies". Criteria 4 grants a waiver for an a.i. that is Toxicity Category IV for inhalation provided an extrapolated inhalation MOE (based on an oral NOAEL) exceeds a target MOE of $\geq$ 1000. Both the a.i. and the spray formulation were tested for acute inhalation toxicity and both materials are classified as Category IV based on their inhalation LC50 values (>2mg/l). The inhalation MOE of flonicamid, extrapolated from the oral

NOAEL, exceeds the target MOE of 1000 for short-term, intermediate-term and chronic exposure. Based on the inhalation category and the extrapolated MOE, flonicamid meets Criteria 4 of the SOP guidance document. References and study summaries are provided in the document. No worksheet. (Silva, 2/7/05)

52964 - 059 216033 "Waiver Request for a 90-Day Inhalation Toxicity Study in Rats on Technical Flonicamid Insecticide For Use on Greenhouse Ornamentals and Interiorscapes," (Li, K.L.; FMC Corporation, Agricultural Products Group, Princeton, NJ; Document #: IB-2003-MB-001-01; 12/24/03) This document contains a request that the requirement for a 90-day inhalation toxicity study in rats be waived. According to the report the USEPA Health Effects Division (HED) assessed the occupational and residential risk of flonicamid and the end-use product F1785 GH 50WG Insecticide for use on greenhouse ornamentals and interiorscapes. The Division identified a 90-day inhalation study in rats as a conditional data gap/requirement. ISK Biosciences Corporation requests that the study be waived based on the HED Standard Operating Procedure entitled "Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies". Criteria 4 grants a waiver for an a.i. that is Toxicity Category IV for inhalation provided an extrapolated inhalation MOE (based on an oral NOAEL) exceeds a target MOE of $\underline{\geq}$ 1000. The HED risk assessment document verifies that flonicamid belongs to Category IV for inhalation toxicity and that the short- and intermediate-term inhalation MOEs far exceed 1000. Based on the HED risk assessment, Technical Flonicamid Insecticide and its end-use WDG formulation meet the waiver criteria, obviating the need for a 90-day inhalation study in rats. (Silva, 2/7/05) No worksheet.